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Sorry, an oversight on my part. Thank you!

Terry

COMPLETED

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Immediate vs Delayed Catheterization and Angioplasty Following Thrombolytic Therapy for Acute Myocardial Infarction

TIMI II A Results

The TIMI Research Group

The Thrombolysis in Myocardial Infarction II A Study investigated whether immediate cardiac catheterization with percutaneous transluminal coronary angioplasty (PTCA), when appropriate, would confer an advantage over the same procedures performed 18 to 48 hours later. All patients were treated with intravenous recombinant tissue–type plasminogen activator within four hours of the onset of acute myocardial infarction. Percutaneous transluminal coronary angioplasty of the infarct-related artery was attempted in 72% of the 195 patients assigned to immediate PTCA; 84% of the attempts were judged to have shown improvement. Percutaneous transluminal coronary angioplasty was attempted in 55% of the 194 patients assigned to 18- to 48-hour PTCA; 93% of the attempts were judged to have shown improvement. No differences between the two PTCA groups were observed for ejection fraction (primary end point), measured by contrast ventriculography predischarge (50.3% in the immediate and 49.0% in the delayed PTCA groups). Immediate catheterization/angioplasty was associated with increased frequency of bleeding and coronary artery bypass surgery. These findings indicate that immediate performance of coronary arteriography and PTCA compared with delaying these procedures for 18 to 48 hours provides no advantage and may be harmful.

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DESPITE a 42% decline in age-adjusted coronary mortality in the past two decades, coronary heart disease still resulted in 524 000 deaths[1] and 758 000 hospital admissions[2] for acute myocardial infarction in the United States in 1986. The precipitating event in patients with myocardial infarction who present with chest pain and ST-segment elevation is, in most instances, the formation of an occlusive coronary thrombus.[3,4] Early treatment with thrombolytic therapy reduces subsequent short-term mortality.[5-7] However, after successful thrombolysis many patients are left with a critically narrowed, infarct-related coronary artery, and the incidence of early reocclusion has exceeded 20% in several series.[4,5,8,9] The optimum subsequent treatment of patients who have received thrombolytic therapy is unclear at present. Specifically, it is unknown whether the instability in the coronary lesion that led to the original coronary closure is influenced favorably by percutaneous transluminal coronary angioplasty (PTCA) to consolidate the initial advantage gained by thrombolytic reperfusion.

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The Thrombolysis in Myocardial Infarction (TIMI) Research Group has designed a trial (TIMI II) to assess the role of PTCA in patients treated with intravenous recombinant tissue–type plasminogen activator (rt-PA) within four hours of the onset of acute myocardial infarction.[10] The overall TIMI II Study involves random assignment to routine coronary arteriography and PTCA (when the anatomy is suitable) 18 to 48 hours after trial entry or to no angiography or PTCA unless symptoms or evidence of uncontrolled spontaneous or provokable ischemia develop. The primary end point is survival free of recurrent infarction at six weeks.[10]

For editorial comment see p 2894.

A substudy (TIMI II A) was incorporated into this overall design to determine whether immediate catheterization and PTCA would confer an advantage over the same procedures performed 18 to 48 hours later.[10] The TIMI II A Study was carried out at seven of the 50 TIMI hospitals; the TIMI II A sites were selected on the basis of extensive experience with PTCA and the requisite logistical support to conduct immediate PTCA. Patients were randomly assigned to one of three treatment strategies after intravenous rt-PA treatment: (1) immediate coronary arteriography followed by PTCA, (2) 18- to 48-hour arteriography with PTCA, or (3) no PTCA unless required by evidence of spontaneous or

provokable ischemia. Patients in all three groups were to have coronary arteriography and ventriculography prior to hospital discharge. Unlike the main study, the primary end point for TIMI II A was ventricular function at the time of hospital discharge.

This article summarizes in-hospital observations on TIMI II A patients assigned to immediate compared with 18- to 48-hour catheterization and PTCA. This early report, comparing two of the three treatment groups, was prompted by two considerations: (1) comparing two groups, both intended to receive intervention with PTCA, would not impinge on the primary comparison of intervention vs no intervention and (2) the TIMI Safety and Data Monitoring Committee encouraged an early report of the excess of untoward events in the immediate PTCA group.

PATIENTS AND METHODS

Study Objectives

The primary objective of TIMI II A was to compare the effects of PTCA performed within two hours vs 18 to 48 hours after the initiation of thrombolytic therapy on resting global left ventricular ejection fraction, measured by contrast ventriculography prior to hospital discharge. It was determined that approximately 200 patients in each treatment group would be required to detect a three-unit difference in global left ventricular function with 85% power. Other variables used to assess these two PTCA groups were clinical outcome in the hospital (including death and recurrent myocardial infarction) and measures of PTCA performance (including suitability, success, and complications). The study protocol was approved by the committees on human research of each participating institution.

Eligibility Criteria

Men and women younger than 76 years of age with ST-segment elevation of at least 0.1 mV in two anatomically contiguous leads and with 30 minutes of chest pain suggestive of acute myocardial ischemia were assessed for eligibility. Patients were eligible only if treatment with rt-PA could be started within four hours of the onset of the chest pain that precipitated hospital admission and if the patient gave consent to participate after the study goals, procedures, and risks were explained. Patients were excluded if they had any one of the following: the inability to give informed consent, PTCA within the preceding six months, prior coronary artery bypass surgery or prosthetic heart valve placement, a history of cerebral vascular disease or uncontrolled hypertension, a bleeding disorder (including significant gastrointestinal tract bleeding), severe trauma within six months, recent prolonged cardiopulmonary resuscitation, or other serious illnesses.

Thrombolytic Therapy

The rt-PA used in this study was produced by the suspension culture method (G11044, Genentech Inc, South San Francisco, Calif) and is the same preparation that is now commercially available. The rt-PA dose initially employed was 150 mg, administered over six hours, as outlined elsewhere[10]; however, because of an unacceptable rate of bleeding complications, particularly the occurrence of intracranial hemorrhage,[11,12] the dose was subsequently reduced to 100 mg given over six hours, consisting of a 6-mg bolus followed by 54 mg in the first hour, 20 mg in the second hour, and 5 mg in each of four additional hours.

PTCA Performance

Patients assigned to immediate PTCA underwent coronary angiography and ventriculography within 120 minutes of the commencement of rt-PA infusion. Percutaneous transluminal coronary angioplasty was performed during the same procedure, whether the infarct-related artery was open or closed, when the coronary anatomy was suitable. Patients assigned to delayed PTCA were scheduled for coronary angiography and ventriculography within 18 to 48 hours after the initiation of the rt-PA infusion. In this group, PTCA was performed during the same procedure, when coronary anatomy was suitable, but only if the infarct-related artery was open, that is, if it had TIMI grade 2 (full perfusion with slow flow) or grade 3 (full perfusion with normal flow) perfusion, as assessed according to previously published criteria.[8] A closed artery was defined as TIMI grade 0 (no flow) or grade 1 (dye penetration without perfusion).[8] Coronary artery bypass graft surgery was limited to patients with pressing clinical indications such as unrelenting ischemic pain or specific coronary artery anatomy unsuitable for PTCA but well suited for surgery, such as left main coronary artery with stenosis of 70% or greater.

Percutaneous transluminal coronary angioplasty of the infarct-related artery was to be performed unless the residual stenosis was less than 60% or this lesion exhibited unsuitable features, such as a length greater than or equal to 20 mm, involvement of bifurcation, distal position, or location beyond a tortuous proximal vessel. Percutaneous transluminal coronary angioplasty also was contraindicated if abrupt closure of the involved vessel would likely cause catastrophic hemodynamic consequences, for example, if the infarct-related artery was significantly narrowed and was functionally equivalent to the left main coronary artery and total occlusion could be expected to result in cardiogenic shock and possibly death.

The success of angioplasty was evaluated visually by the angioplasty operator. *Full improvement* required normal or improved post-PTCA flow in the infarct-related artery and both an absolute reduction in lumen stenosis by greater than or equal to 20% and a final lumen stenosis of less than 60%. *Partial improvement* was defined as unchanged or improved flow and only one of the above changes in lumen stenosis.

All coronary angiograms were reviewed, without knowledge of the treatment assignment, by senior cardiologists in the radiographic core laboratory to determine the suitability of the lesion(s) of the infarct-related artery for coronary angioplasty and, using the previously mentioned definitions, to assess the success of angioplasty if performed. In addition to these qualitative visual assessments, the degree of stenosis and minimum diameter of the infarct-related artery were measured quantitatively by a method described previously.[13] Results of the quantitative measurements will be presented in a subsequent report.

Concomitant Care

All patients were given lidocaine hydrochloride (a bolus of 1 to 1.5 mg/kg followed by 2 to 4 mg/min for a minimum of 24 hours) and were treated according to the general guidelines outlined in the TIMI II protocol.[10] Continuous intravenous heparin administration at 1000 U/h was begun one hour after an initial 5000-U bolus was given at the initiation of rt-PA infusion. The heparin infusion was adjusted thereafter to maintain an activated partial thromboplastin time between 1.5 and two times the upper limit of normal. Heparin administration was continued until the fifth hospital day unless the patient had serious bleeding. The heparin protocol was modified for patients assigned to 18- to 48-hour PTCA as follows: the heparin infusion was decreased by 50% two or three hours before catheterization; at catheterization, a bolus of 5000 US Pharmacopeia units was administered after insertion of the arterial sheath; the heparin infusion at full dose was resumed within one hour of the bolus in the catheterization laboratory and continued for 48 hours.

Aspirin, 80 mg/d, was administered starting on day 2 and was increased to 325 mg/d on day 5 when heparin therapy was discontinued. All patients were monitored carefully for clinical events during the first few days as outlined elsewhere.[8,10] Recurrent myocardial ischemia or infarction was reported by the clinical investigators when the patient experienced prolonged chest pain, characteristic electrocardiographic changes, or cardiac enzyme changes. The Mortality and Morbidity Classification Committee (expert cardiologists who are not TIMI clinical center investigators) reviewed all reported events without knowledge of treatment assignment and, following criteria established prior to the start of the classification of these events, classified the reported events as definite myocardial infarction, recurrent ischemia, or no event. The definitions used to classify these events are given in Table 1.

Table 1.—Definitions Used to Classify Events*

Events reported by clinical center investigators that occur 18 h or more after study entry are considered definite nonfatal recurrent myocardial infarction if one of the following criteria are met:
- Enzyme changes
  - CK is collected routinely over the first 10 d (every 4 h for 24 h, every 6 h for the next 24 h, and then daily for 8 d or until hospital discharge) of enrollment in the Thrombolysis in Myocardial Infarction II Study, but only on indication (usually pain) thereafter
    - If the CK MB or CK levels are greater than two times the upper limit of normal and increase by 25% over the previous value; qualitative CK MB must be positive when available, and CK MB takes precedence over CK
    - If CK MB or CK are less than two times the upper limit of normal, increase by 50% over the previous value, and exceed the upper limit of normal by at least 50%; qualitative CK MB results must be positive when available, and CK MB takes precedence over CK
- Electrocardiogram (ECG)
  - Major new Q waves in at least two or more leads or new left bundle-branch block in the absence of any previous left branch conduction defect
- Committee vote
  - Failing independent classification by two members of the MMCC according to enzyme or electrocardiographic criteria, a simple majority vote of MMCC members (chairman casts tiebreaking votes) at a meeting of the committee as a whole

Events reported by clinical center investigators that occur less than 18 h after study entry. The following definitions apply:
- Pain: more than 20 min of new or markedly worse chest pain
- Electrocardiogram
  - New ST-segment depression or elevation ≥2 mm (0.2 mV) in at least two contiguous leads or
  - Elevation of ST segment ≥2 mm (0.2 mV) above ST segments prior to the onset of pain (last electrocardiogram)
- Enzyme changes
  - Appropriately timed increase of at least 33% following a 25% decrease (peak to valley) for values greater than two times the upper limit of normal
  - Appropriately timed increase of at least 100% following a 50% decrease for values less than two times the upper limit of normal

Events that occur less than 18 h after study entry are classified as follows:

Classes	Pain	ECG	CK
No recurrent event	+	−	−
Recurrent ischemic event	+	+	−
Nonfatal myocardial infarction	+	±	+

*CK indicates creatine kinase; CK MB, an isoenzyme of CK that contains M and B subunits; and MMCC, Mortality and Morbidity Classification Committee.

Randomization and Treatment Allocation

Patients were assigned to treatment based on randomization schedules prepared for each clinical center by the coordinating center staff. These schedules were designed to provide balance in the number of patients assigned to each of the PTCA groups and to the no PTCA group within each clinical center. The randomization schedule was stored in a personal computer system at each clinical center. After a patient was judged eligible for the study, the treatment assignment for this patient was obtained by entering identification data and information on eligibility. If this information passed computer edit checks, the next available treatment assignment was printed out by software developed for this study in the coordinating center. (Early in the study, the clinical center staff selected the next available sealed treatment allocation envelope to obtain treatment assignment.)

Statistical Considerations

One analysis of radiographic left ventricular ejection fraction data at hospital discharge (the primary end point) was based only on the results for patients who had hospital discharge contrast ventriculography. A second analysis also was performed to estimate the effect of missing data. In this analysis, patients who died before the predischarge ventriculogram could be obtained were assigned an ejection fraction of zero, and patients who had only radionuclide studies prior to discharge had radiographic ejection fraction estimated based on the resting radionuclide study. The relationship of ejection fraction (EF) estimated by contrast radiography and by resting radionuclide (RVG) procedures was determined based on 253 patients with both studies in TIMI II Pilot Study and Phase II and was found to be the following:

$$\text{Contrast EF} = 18.309 + 0.638 \text{ rest RVG EF}$$

Variable	SE	P
Intercept	2.11	.0001
Slope	0.04	.0001

$$R^2 = .48$$

The study protocol specified that the primary and secondary end points would be evaluated for subgroups of patients defined by (1) site of infarct, (2) time of onset of pain, and (3) risk group. *Not low-risk patients* were defined as those with one or more of the following risk factors: (1) history of previous myocardial infarction, (2) ST-segment elevation in anterior electrocardiographic leads, (3) rales extending upwards to cover more than one third of the lung fields, (4) hypotension (systolic blood pressure, <100 mm Hg) and sinus tachycardia (atrial rate, >100 beats per minute), (5) atrial fibrillation or flutter, and (6) age 70 years or older.

The statistical testing of differences in mean ejection fraction for the defined treatment comparisons in this study was based on the two-sample test of means.[14] An analysis of median ejection fraction also was performed using the Wilcoxon rank-sum test (with normal approximation).[14] For ejection fraction, $P<.05$ (for a two-sided test) was considered statistically significant. The two PTCA groups also were compared with respect to other end points, mortality, mortality or recurrent myocardial infarction, bleeding complications, and other clinical events. To adjust for multiple testing (which increases the likelihood of observing a difference with $P<.05$ although there is no true difference), $P<.01$ (for a two-sided test) was specified for treatment comparisons of clinical events.[15] In all of the analyses in this study, patients were included in the group to which they were randomized originally, whether or not PTCA was actually performed within the time specified for that treatment group. The results presented in this report are based on all data processed in the TIMI coordinating center as of Feb 23, 1988.

The TIMI Safety and Data Monitoring Committee reviewed extensive reports at scheduled meetings during the course of the study. These reports, prepared by the coordinating center, contained data relating to all end points under surveillance.

RESULTS

Enrollment

A total of 389 patients were enrolled from April 1986 through September 1987; one hundred ninety-five were randomly assigned to immediate PTCA and 194 to 18- to 48-hour PTCA. Approxi-

mately one third of the patients in each PTCA group (62 in the immediate and 66 in the 18- to 48-hour groups) received 150 mg of rt-PA, and two thirds (133 in the immediate and 128 in the 18- to 48-hour groups) received 100 mg of rt-PA.

Baseline Characteristics

The majority of TIMI II A patients were men (83%) and were white (98%). The mean age was 57 years. The time from onset of symptoms to initiation of thrombolytic therapy ranged from 30 minutes to four hours, and the mean time was 2.9 hours (Table 2). Despite randomization, more patients in the immediate (two-hour) PTCA group than in the 18- to 48-hour PTCA group (72.8% vs 61.9%, respectively) were classified as not low risk.

Angiographic Findings

Two of the 195 patients assigned to immediate PTCA did not have cardiac catheterization and PTCA performed: one patient refused and the treatment assignment was misinterpreted for another. Nineteen of the 194 patients in the 18- to 48-hour PTCA group did not have catheterization (Tables 3 and 4). The most common reasons for catheterization not being performed in the specified period in the latter group were a prior emergency procedure (PTCA [eight patients], coronary artery bypass graft surgery [one patient], and cardiac catheterization only [two patients]), death before 18 hours (five patients), or some other event (one patient each with fever, hemodynamic instability, or insufficient evidence of myocardial infarction).

Time from initiation of rt-PA infusion to catheterization averaged 1.4 hours (range, 15 minutes to 3.3 hours) in the immediate PTCA group and 32.7 hours (range, 16 to 57 hours) in the 18- to 48-hour PTCA group. The patency rates for the infarct-related artery on the initial angiogram are given in Table 3. Overall, 75% of patients had an open infarct–related artery at two hours and 83% had an open infarct–related artery at 18 to 48 hours. Patency rates did not differ between the 150-mg and the 100-mg treatment regimens within either of the two PTCA treatment groups (Table 3).

The number of vessels with stenosis of greater than 60% before PTCA was assessed by radiographic core laboratory staff. About 5% of patients had no vessels with stenosis greater than 60% at 1.4 hours after the start of rt-PA infusion (or after the infusion of approximately 76 mg of the 100-mg dose) compared with 14.6% at 32.7 hours (Table 3). Only 5% of patients had three or more vessels with stenosis of 60% or more at the later time.

Table 2.—Baseline Characteristics of TIMI II A Patients*

Characteristic	Percent of Patients: 2-h PTCA Group (N = 195)	Percent of Patients: 18- to 48-h PTCA Group (N = 194)
Sex, M	83.6	82.5
Race, White	99.0	96.4
Mean age, y	57.4	56.3
Now low risk	72.8	61.9
Age 70 + y	16.4	11.3
Prior myocardial infarction	19.5	15.0
Anterior myocardial infarction	56.9	47.4
Rales ≥⅓ of lung fields	4.1	2.1
Hypotension and sinus tachycardia	2.1	5.2
Atrial fibrillation or flutter	3.1	1.0
Other risk factors		
History of angina	56.9	56.2
History of congestive heart failure	2.1	3.1
History of hypertension	45.4	44.3
History of diabetes mellitus	11.8	10.4
Infarct-related artery (clinic)		
Right coronary artery	39.1	45.4
Left anterior descending	47.9	36.2
Circumflex	12.0	18.4
Left main coronary artery	1.0	0.0
No. unavailable	1	1
Ongoing chest pain at recombinant tissue–type plasminogen activator initiation	85.1	86.6
Mean ± SE time from onset of pain to study entry, h	2.8 ± 0.06	2.9 ± 0.06

*TIMI indicates Thrombolysis in Myocardial Infarction; and PTCA, percutaneous transluminal coronary angioplasty.

Table 3.—Angiographic Findings Before Percutaneous Transluminal Coronary Angioplasty (PTCA)

Angiographic Finding	No. (%) of Patients: 2-h PTCA Group	No. (%) of Patients: 18- to 48-h PTCA Group
Patency of infarct-related artery		
Recombinant tissue-type plasminogen activator dose, mg		
150	47/62 (76)	52/61 (85)
100	98/131 (75)	93/114 (82)
Total	**145/193 (75)**	**145/175 (83)**
Mean ± SE time to catheterization, h	1.4 ± 0.04	32.7 ± 0.7
No. of vessels ≥60% stenosis (core laboratory reading)		
0	9 (4.9)	24 (14.6)
1	105 (57.1)	96 (58.5)
2	42 (22.8)	36 (22.0)
3	28 (15.2)	8 (4.9)
No. missing data	9	11
No. of patients	184	164

PTCA Performance

Coronary angioplasty was attempted in 141 (72%) of the 195 patients assigned to the immediate PTCA group and 107 (55%) of the 194 patients assigned to 18- to 48-hour PTCA. The lesion in the infarct-related artery could not be crossed by the dilatation catheter in five patients in the immediate PTCA group and two patients in the 18- to 48-hour PTCA group (Table 4). Of the 141 patients in the immediate PTCA group in whom PTCA was attempted, 119 (84.4%) were judged by the angioplasty operator to have shown improvement; information on improvement was not available for one patient since the infarct-related artery was not filmed after PTCA. Of the 107 patients in the 18- to

Table 4.—PTCA Performance Among TIMI II A Patients*

Performance	No. (%) of Patients	
	2-h PTCA Group (N=195)	18- to 48-h PTCA Group (N=194)
No PTCA	54 (27.7)	87 (44.8)
No catheterization	2 (1.0)	19 (9.8)
Catheterization only	52 (26.7)	68 (35.0)
Reason no PTCA		
No lesion	19 (9.7)	28 (14.4)
Unsuitable	32 (16.4)	15 (7.7)
Closed	0 (0.0)	24 (12.4)
Other	1 (0.5)	1 (0.5)
PTCA	141 (72.3)	107 (55.2)
Failure to cross	5	2
Improved		
Open infarct artery before PTCA†	85/104 (81.7)	95/100 (95.0)
Closed infarct artery before PTCA†	34/37 (91.9)	5/7 (71.4)
Total	119/141‡(84.4)	100/107 (93.5)

*PTCA indicates percutaneous transluminal coronary angioplasty; and TIMI, Thrombolysis in Myocardial Infarction.
†Open, TIMI grade 2 or 3; and closed, TIMI grade 0 or 1.
‡Infarct-related artery not filmed after PTCA in one patient, and this patient was classified as not improved.

Table 5.—Complications Associated With Cardiac Catheterization and PTCA*

Complication	No. (%) of Patients		
	2-h PTCA Group	18- to 48-h PTCA Group	P
All patients with catheterization	193 (100.0)	175 (100.0)	...
Complications of cardiac catheterization†	10 (5.2)	2 (1.1)	.03
Any complication of catheterization or PTCA for patients with catheterization	24 (12.4)	7 (4.0)	.004
Patients with PTCA attempted	141 (100.0)	107 (100.0)	...
Any immediate complications	18 (12.8)	7 (6.5)	.11
Total occlusion—any‡	16 (11.4)	5 (4.7)	.06
Infarct-related artery	11 (7.8)	3 (2.8)	...
Branch of infarct-related artery	4 (2.8)	2 (1.9)	...
Other major artery	1 (0.7)	0 (0.0)	...
Emergency coronary artery bypass graft surgery	1 (0.7)	1 (0.9)	...
Reinfarction	2 (1.4)	1 (0.9)	...
Death	0 (0.0)	1 (0.9)	...
Other	4 (2.8)	1 (0.9)	...
Complications within 24 h of PTCA for patients with PTCA§			
Death	3 (2.1)	1 (1.0)	...
Myocardial infarction	4 (2.8)	3 (2.8)	...
Coronary artery bypass graft surgery	6 (4.3)	2 (1.9)	...
Any of the above	12 (8.5)	4 (3.7)	.13

*PTCA indicates percutaneous transluminal coronary angioplasty.
†Includes new occlusion of coronary artery or branch, arrhythmia, and/or clinical complications, including pulmonary edema, hypotension, cardiac arrest, and anaphylaxis.
‡Patients also may have had an occlusion reported as a complication of cardiac catheterization.
§Includes immediate complications.

48-hour PTCA group in whom PTCA was attempted, 100 (93.5%) were judged to have shown improvement.

Reasons for not performing PTCA in association with cardiac catheterization are shown in Table 4. The protocol precluded dilatation of a closed infarct–related artery for patients assigned to 18- to 48-hour PTCA, except for those with compelling clinical indications, while it was encouraged for patients assigned to the immediate procedure. The percentage of patients with no lesion greater than or equal to 60% was judged to be 9.7% in the immediate PTCA group and 14.4% in the 18- to 48-hour PTCA group. This percentage for the immediate group is higher than the 5% reported by the radiographic core laboratory staff to have no vessel with stenosis greater than or equal to 60% (Table 3). Of the 32 patients who did not have PTCA performed because of unsuitable anatomy in the immediate PTCA group, nine had a closed infarct–related artery; one patient who did not have PTCA performed for other reasons also had a closed infarct–related artery.

The radiographic core laboratory visual assessment of suitability for PTCA confirmed that the coronary anatomy met the protocol criteria for suitability in 93% of patients who had the assigned PTCA performed and confirmed that the coronary anatomy was not suitable in 49% of patients who did not have the assigned PTCA. The overall agreement on PTCA suitability was 79%, reflecting the fact that the decision to perform PTCA was not determined solely on the assessment of the coronary anatomy but also took into consideration the patient's clinical condition at the time of the angiographic assessment. The agreement on degree of improvement between the angioplasty operator who performed the PTCA and the radiographic core laboratory assessment was 91%; that is, both assessments indicated improvement (either full or partial) or no improvement following PTCA performance.

There were more complications associated with cardiac catheterization in the immediate PTCA group (10/193, 5.2%) than in the 18- to 48-hour PTCA group (2/175, 1.1%) (Table 5) and more acute complications during the PTCA in the immediate group vs the 18- to 48-hour group (18/141, 12.8% vs 7/107, 6.5%). New occlusion of a coronary artery or branch was observed during baseline angiography in five patients (2.6%) and during or immediately after PTCA in 14 additional patients (7.3%) in the immediate PTCA group compared with one patient (0.6%) during catheterization and four additional patients (2.3%) during PTCA in the 18- to 48-hour PTCA group. Three deaths occurred in the immediate PTCA group and one death occurred in the 18- to 48-hour PTCA group within 24 hours of completing the procedure (Table 6). The number of patients with one or more adverse events within the first 72 hours after initiation of rt-PA treatment in the immediate PTCA group was 42 (21.5%) and in the 18- to 48-hour PTCA group was 27 (13.9%) ($P=.05$). These adverse events in the first 72 hours included death, confirmed recurrent myocardial infarction, transfusion of more than 1 U of whole blood or packed red blood cells (without coronary artery bypass surgery), coronary artery bypass surgery after a protocol PTCA or repeated PTCA in either PTCA group and, in addition, for the 18- to 48-hour PTCA

Table 6.—All Patient Deaths Within 21 Days of Study Entry*

Patient Number	Protocol PTCA Done	Nonprotocol PTCA or Coronary Artery Bypass Graft (CABG) Surgery	Recurrent Myocardial Infarction	Time to Death	Cause of Death
		Patients Assigned to Immediate PTCA			
1	Attempted	No	No	3 h	ACHD
2	No	No	Yes	4 h	ACHD
3	No	No	No	5 h	ACHD
4	Attempted	No	No	9 h	Gastrointestinal tract hemorr
5	Yes	No	No	12 h	ACHD
6	No	No	No	21 h	Stroke
7	No	No	No	23 h	ACHD
8	No	CABG	No	30 h	Cardiovascular surgery
9	Yes	PTCA	Yes	31 h	ACHD
10	No	No	No	4 d	ACHD
11	Yes	No	No	4 d	ACHD
12	Yes	CABG	No	5 d	ACHD
13	Yes	CABG	No	7 d	ACHD
14	No	No	No	18 d	Cardiac arrest
		Patients Assigned to 18- to 48-h PTCA			
1	No	No	No	2 h	ACHD
2	No	No	No	2 h	ACHD
3	No	No	No	5 h	ACHD
4	No	PTCA	Yes	7 h	ACHD
5	No	No	No	25 h	Stroke
6	Yes	No	Yes	48 h	ACHD
7	Yes	No	Yes	60 h	ACHD
8	Yes	No	No	3 d	ACHD
9	Yes	No	No	8 d	ACHD
10	No	No	No	8 d	ACHD
11	No	PTCA	No	17 d	ACHD

*PTCA indicates percutaneous transluminal coronary angioplasty; and ACHD, atherosclerotic cardiovascular heart disease.

Table 7.—Predischarge Contrast Ejection Fraction

	Ejection Fraction, %				
	Observed			Imputed*	
	2-h PTCA Group	18- to 48-h PTCA Group	P†	2-h PTCA Group	18- to 48-h PTCA Group
		No. (Mean)			
All patients	150 (50.3)	148 (49.0)	.37	185 (46.4)	180 (46.7)
Low-risk patients	43 (52.2)	57 (52.1)	.96	50 (50.4)	68 (51.5)
Not low–risk patients	107 (49.5)	91 (47.2)	.18	135 (45.0)	112 (43.7)
No prior myocardial infarction	125 (51.0)	125 (49.7)	.39	151 (47.4)	154 (46.8)
Prior myocardial infarction	25 (46.8)	23 (45.5)	.72	34 (42.0)	26 (45.9)
Anterior myocardial infarction	82 (49.0)	71 (46.0)	.12	106 (43.8)	85 (42.6)
No anterior myocardial infarction	68 (51.8)	77 (51.9)	.95	79 (50.0)	95 (50.3)
		SE			
All patients	0.9	1.0	...	1.2	1.2
Low-risk patients	1.4	1.4	...	1.9	1.4
Not low–risk patients	1.1	1.4	...	1.5	1.7
No prior myocardial infarction	0.9	1.2	...	1.3	1.4
Prior myocardial infarction	2.6	2.4	...	3.3	2.1
Anterior myocardial infarction	1.2	1.6	...	1.7	1.9
No anterior myocardial infarction	1.3	1.3	...	1.6	1.4
		No. (Median)			
All patients	150 (51)	148 (50)	.32	185 (50)	180 (49.8)

*Total number of imputations made: two-hour group (35 patients), 14 deaths and 21 estimated from radionuclide study; 18- to 48-hour group (32 patients), ten deaths and 2 estimated from radionuclide study.

†A two-sample test of means is used to test the hypothesis of no difference in the means between the groups[14]; a Wilcoxon rank-sum test (with normal approximation) used to test the hypothesis of no difference in medians between the groups.[15]

Table 8.—Clinical Events Within 21 Days of Study Entry

Clinical Event*	No. (%) of Patients: 2-h PTCA Group	18- to 48-h PTCA Group	P
All patients	N=195	N=194	...
Death	14 (7.2)	11 (5.7)	.54
Fatal and nonfatal reinfarction	13 (6.7)	8†(4.1)	.27
Death or reinfarction	25 (12.8)	17 (8.8)	.20
Intracranial hemorrhage	1 (0.5)	1 (0.5)	1.00
CABG after PTCA	13 (6.7)	3 (1.5)	.02
Transfusion >1 U	39 (20.0)	14 (7.2)	<.001
With CABG	17 (8.7)	8 (4.1)	.06
Without CABG	22 (11.3)	6 (3.1)	.002
One or more of above	60 (30.8)	29 (14.9)	<.001
All CABG	32 (16.4)	15 (7.7)	.01
CABG without PTCA	19 (9.7)	12 (6.2)	.26
Low-risk patients	n=53	n=74	...
Death	2 (3.8)	2 (2.7)	.73
Fatal and nonfatal reinfarction	1 (1.9)	1 (1.4)	.81
Death or reinfarction	3 (5.7)	3 (4.1)	.67
Intracranial hemorrhage	0 (0.0)	1 (1.4)	1.00
CABG after PTCA	3 (5.7)	2 (2.7)	.65
Transfusion >1 U	6 (11.3)	7 (9.5)	.73
With CABG	1 (1.9)	5 (6.8)	.20
Without CABG	5 (9.4)	2 (2.7)	.10
One or more of above	10 (18.9)	10 (13.5)	.46
All CABG	5 (9.4)	7 (9.5)	1.00
CABG without PTCA	2 (3.8)	5 (6.8)	.70
Not low-risk patients	n=142	n=120	...
Death	12 (8.4)	9 (7.5)	.78
Fatal and nonfatal reinfarction	12 (8.5)	7 (5.8)	.42
Death or reinfarction	22 (15.5)	14 (11.7)	.37
Intracranial hemorrhage	1 (0.7)	0 (0.0)	1.00
CABG after PTCA	10 (7.0)	1 (0.8)	.01
Transfusion >1 U	33 (23.2)	7 (5.8)	<.001
With CABG	16 (11.3)	3 (2.5)	.01
Without CABG	17 (12.0)	4 (3.3)	.01
One or more of above	50 (35.2)	19 (15.8)	<.001
All CABG	27 (19.0)	8 (6.7)	.003
CABG without PTCA	17 (12.0)	7 (5.8)	.13

*CABG indicates coronary artery bypass graft surgery; and PTCA, percutaneous transluminal coronary angioplasty.
†Includes one patient who had a heart transplant.

group, any emergency procedure (PTCA, coronary artery bypass surgery, or catheterization only) performed prior to 18 hours after entry.

Global Left Ventricular Function

Predischarge contrast ventriculography was available for 77% of all patients in the immediate PTCA group and 76% of all patients in the 18- to 48-hour PTCA group or 83% (150/181) and 80% (148/184), respectively, of patients who were discharged alive or who survived for 21 days in the hospital. There was no difference between treatment groups for mean or median ejection fractions based on patients who had predischarge contrast ventriculography (Table 7). With imputations of predischarge ejection fraction as described in the "Methods" section for patients who did not have contrast ventriculograms, data are available for 95% of the patients in the immediate PTCA group and 93% of those in the 18- to 48-hour PTCA group. This analysis also showed no difference between the two PTCA groups in mean or median ejection fractions.

Because of the previously noted imbalance between the PTCA groups in the proportion of patients who were not low risk at the time of entry, mean ejection fractions also were calculated separately for low-risk patients as well as for not low-risk patients within each treatment group. No differences between the two PTCA treatment groups were observed for mean ejection fraction whether or not missing values were imputed.

Patency of the Infarct-Related Artery Prior to Hospital Discharge

In both PTCA groups, 78% of all randomized patients had coronary arteriography before hospital discharge (152 of 195 in the immediate group and 151 of 194 in the 18- to 48-hour group). The primary reasons coronary arteriography was not performed prior to hospital discharge were patient (or patient's physician) refusal (nine in the immediate PTCA group and 15 in the 18- to 48-hour PTCA group), death (14 in the immediate group and ten in the 18- to 48-hour group), prior procedure (nine in the immediate group and 12 in the 18- to 48-hour group) and other (11 in the immediate group and six in the 18 to 48-hour group). Of those who were restudied, 119 and 121 patients (78% and 80%) in the immediate and 18- to 48-hour PTCA groups, respectively, had an open infarct-related artery; 26 and 22 patients (17% and 15%) in each of these PTCA groups had a closed infarct-related artery, and the infarct-related artery was not studied in seven patients (5%) in the immediate group and eight patients (5%) in the 18- to 48-hour group. Of the 50 patients with no predischarge patency data in the immediate PTCA group, 14 died prior to hospital discharge, one had a confirmed recurrent myocardial infarction, 14 had coronary artery bypass surgery, and two had closed infarct-related artery prior to performance of a nonprotocol PTCA. Of the 51 patients without data in the 18- to 48-hour PTCA group, ten died, two had a confirmed myocardial infarction, 13 had coronary artery bypass surgery, and five had closed infarct-related artery prior to nonprotocol PTCA. If all these patients were classified as having closed infarct-related arteries, the number of patients with closed infarct-related arteries was 57 (32%) of 176 in the immediate PTCA group and 52 (30%) of 173 in the 18- to 48-hour PTCA group. Of the remaining patients for whom patency status prior to hospital discharge was not available, 18 of 19 in the immediate PTCA group and 17 of 21 in the 18- to 48-hour PTCA group had either an open infarct-related artery at the end of the cardiac catheterization following protocol PTCA or had no lesion greater than or equal to 60% and PTCA was not performed.

Clinical Events

The number of deaths in each treatment group is given in Table 8. Information on cause of death and other characteristics of patients who died are given in Table 6. The percentage of patients who died within the first 21 days was not different in the two PTCA groups (7.2% vs 5.7% in the immediate vs the 18- to 48-hour PTCA groups). Within the first 24 hours, the number of deaths in the immediate PTCA group was seven (3.6%) and the number in the 18- to 48-hour PTCA group was four (2.1%)

($P = .35$); the number of deaths in the first 72 hours in each group was nine (4.6%) and seven (3.6%), respectively ($P = .60$).

Other clinical events that occurred within the first 21 days in each of the PTCA groups are summarized in Table 8. The percentages of fatal and nonfatal recurrent myocardial infarction were not significantly different (6.7% vs 4.1% for recurrent myocardial infarction in the immediate vs 18- to 48-hour PTCA group). Two patients in each of the PTCA groups died within 48 hours of recurrent myocardial infarction. The combined end point, death *or* nonfatal myocardial infarction, occurred in 25 patients (12.8%) in the immediate and 17 patients (8.8%) in the 18- to 48-hour PTCA groups ($P = .20$). Two patients, one in each PTCA group, sustained intracranial hemorrhage and died; both had received 100 mg of rt-PA. More patients in the immediate PTCA group than in the 18- to 48-hour PTCA group (13 compared with three patients; $P = .02$) had coronary bypass surgery within 21 days of the protocol PTCA. Transfusions were more frequent in the immediate PTCA group (both with and without coronary artery bypass surgery), and 30.8% in the immediate PTCA group vs 14.9% in the 18- to 48-hour PTCA group ($P < .001$) had one or more of the previously described events (death, recurrent myocardial infarction, coronary artery bypass surgery after PTCA, or transfusion).

COMMENT

While the overall TIMI II Study was designed to evaluate the potential benefit of routine 18- to 48-hour catheterization and PTCA compared with conservative management following rt-PA administration for acute myocardial infarction, TIMI II A was conducted to evaluate the possibility that an aggressive approach, consisting of treating the patient with a thrombolytic agent and directly transferring him/her to the catheterization laboratory, carrying out coronary arteriography, and performing PTCA if feasible, might be superior to the delayed (18- to 48-hour) angioplasty.

The major findings of this randomized study were that immediate catheterization and angioplasty offered no benefit over delayed (18 to 48 hours after start of thrombolytic therapy) catheterization and angioplasty with respect to global left ventricular function. Moreover, early catheterization/angioplasty was associated with an increased frequency of bleeding and other complications, including emergency coronary artery bypass surgery.

Performance of Angioplasty

An average of 1.4 hours after the initiation of rt-PA therapy, 75% of patients were found on catheterization to have patent infarct-related arteries (TIMI grade 2 or 3) compared with 83% of patients who underwent catheterization an average of 32.7 hours after the initiation of the rt-PA infusion. No differences in infarct-related artery patency at either time point were observed between the two doses (150 mg and 100 mg) of rt-PA used in this study. The Thrombolysis and Angioplasty in Myocardial Infarction Study Group also observed 75% patency of the infarct-related artery at 90 minutes after initiation of rt-PA therapy.[16]

Almost all of the patients assigned to immediate PTCA had cardiac catheterization performed, and approximately 72% were judged by the angioplasty operator to have significant (≥60%) coronary stenosis of the infarct-related artery thought to be amenable to angioplasty (Table 4). The radiographic core laboratory assessment confirmed the decision of the operator in 79% of cases. The TIMI investigators defined significant disease in a coronary artery as greater than or equal to 70% reduction in luminal diameter.[10] Local cineangiographic readings of infarct-related artery stenosis for suitability for PTCA were made in the cardiac catheterization laboratory at the time of initial angiographic evaluation. To ensure that PTCA was attempted for all patients assigned to PTCA who were ultimately found to have significant disease, the TIMI subcommittee of angioplasty operators proposed, and the Steering Committee agreed, to set the stenosis threshold for PTCA performance at 60%.

Of the 141 patients in whom angioplasty was attempted, 84% showed improvement in the lumen diameter of the infarct-related artery according to the clinical center reports. Although 16 patients (8%) assigned to the 18- to 48-hour angioplasty group had an untoward event (five patients died and 11 patients underwent an emergency procedure) that precluded the performance of cardiac catheterization during the scheduled interval, coronary angioplasty was attempted as scheduled in 107 patients (55%) assigned to this therapy, and 93% of these attempts were considered successful. A slightly higher percentage of patients in the 18- to 48-hour PTCA group than in the immediate PTCA group (14% vs 10%) had insignificant (<60%) coronary obstruction when studied. It is important to note the low proportion of patients with multivessel disease: 38% after approximately 1 hours after the start of rt-PA infusion and 27% at 27 hours after the completion of the six-hour infusion of rt-PA, perhaps reflecting that further clot dissolution could occur as a result of receiving the full dose of rt-PA or spontaneous thrombolysis.

A total of 47 (24%) of 193 patients in the immediate PTCA group compared with 31 (18%) of 175 patients in the 18- to 48-hour PTCA group had an occluded infarct-related artery at the time of catheterization. The protocol provided that coronary angioplasty could be performed in the immediate PTCA group whether the artery was open or closed but could not be performed in the 18- to 48-hour PTCA group unless compelling clinical conditions were present. The patients with totally occluded infarct-related arteries in the 18- to 48-hour PTCA group make up most of the difference between the two PTCA groups in the proportions of patients suitable for angioplasty. In the immediate PTCA group, the infarct-related artery was successfully dilated in 34 (92%) of 37 patients with a closed infarct-related artery who had PTCA performed. Only seven (23%) of 31 patients in the 18- to 48-hour PTCA group had angioplasty of a closed infarct-related artery attempted for clinical indications, five (71%) of whom were dilated successfully.

Complication Rates

Cardiac catheterization and/or PTCA at two hours was associated with a higher complication rate than the same procedure at 18 to 48 hours (12.4% vs 4.0%; $P = .004$). There also were more complications during the first 24 hours after a PTCA attempt in the early compared with the later period: 8.5% (12/141) died, had an infarct extension, or required emergency surgery in the immediate PTCA group compared with 3.7% (4/107) in the 18- to 48-hour PTCA group. While 16 (8%) of the 194 patients randomized to 18- to 48-hour PTCA died or had an emergency procedure prior to 18 hours, even adding all these events to those occurring in the first 24 hours after the scheduled cardiac catheterization did not result in a higher overall incidence of adverse events during the first 72 hours after study entry in the 18- to 48-hour PTCA group compared with the immediate PTCA group (21.5% vs 13.9%; $P = .05$).

Ventricular Function

In the analysis of treatment effects on left ventricular ejection fraction, the primary end point of this study, an attempt was made to take into account

two potential sources of bias: missing observations and the slight imbalance in the distribution of high-risk patients between the two treatment groups. All of the analyses showed no differences between the two coronary angioplasty groups.

Occurrence of Bleeding

Bleeding complications were more frequent in the immediate PTCA group compared with the 18- to 48-hour PTCA group and were more frequent with the 150-mg dose of rt-PA than with the 100-mg dose within both of the randomized angioplasty groups. There were two cases of intracranial hemorrhage: one in each of the angioplasty groups. In the TIMI II Pilot Study, intracranial hemorrhage occurred in five (1.5%) of 326 patients who received 150 mg of rt-PA[10]; this observation, in part, led to the change in dosage of rt-PA during TIMI II.[11,12] This change from 150 mg to 100 mg did not substantially change the observed patency rates in TIMI II A patients.

The percentage of patients receiving transfusions (≥2 U) was 20% in the immediate PTCA group compared with 7.2% in the 18- to 48-hour PTCA group. Although in a substantial proportion of patients the transfusions were after coronary artery bypass graft surgery (8.7% in the immediate PTCA group and 4.1% in the 18- to 48-hour PTCA group), 11.3% in the immediate PTCA group and 3.1% in the 18- to 48-hour PTCA group received transfusions of 2 U or more *without* bypass surgery ($P = .002$). Thus, one of the chief risks of early angiography was bleeding at the catheterization site secondary to thrombolytic therapy, concommitant heparinization, and the arterial puncture necessary for catheterization. The changes in coagulation parameters with 150 mg of rt-PA compared with 100 mg of rt-PA have been reported elsewhere.[17]

Clinical Events

There was no statistically significant difference in 21-day mortality in the two angioplasty groups (7.2% in the immediate PTCA group compared with 5.7% in the 18- to 48-hour PTCA group) or in the occurrence of fatal and nonfatal reinfarction (6.7% vs 4.1%, respectively). The proportion of patients with one or more adverse clinical events (an end point not defined prior to conduct of the study but selected after reviewing the data) was 30.8% in the immediate PTCA group compared with 14.9% in the 18- to 48-hour PTCA group ($P < .001$) and was greater among patients classified as not low risk at baseline in both treatment groups.

Other Studies

Results of TIMI II A are consistent with those of the recently reported Thrombolysis and Angioplasty in Myocardial Infarction Study[16] and the European study of an invasive strategy (angiography and PTCA) vs a noninvasive strategy following thrombolysis,[18] although these studies followed different patient selection criteria. The European study, in which angioplasty was attempted in 168 (93%) of 180 patients assigned to invasive strategy, showed a significantly higher mortality in this group compared with the noninvasive strategy group (7% vs 3%). In the Thrombolysis and Angioplasty in Myocardial Infarction Study (unlike TIMI II A), *all* patients underwent immediate coronary angiography, and only those with an open infarct–related artery considered suitable for angioplasty were then randomized to immediate angioplasty or elective angioplasty. Despite this difference in design, results of immediate angioplasty in the Thrombolysis and Angioplasty in Myocardial Infarction Study were similar to those observed for the immediate PTCA group in TIMI II A, and neither study showed a difference in ventricular function between immediate and delayed PTCA. Both studies also showed that patients in the immediate angioplasty group were more likely to require emergency coronary artery bypass graft surgery and/or to experience reocclusion or recurrent ischemic events than patients who have the procedures later.

Summary

In conclusion, the strategy of immediate catheterization and angioplasty did not result in improved global ventricular function and seemed to be associated with a higher risk of adverse clinical events (such as emergency coronary artery bypass surgery, reinfarction, and required transfusions) than the strategy of catheterization and angioplasty 18 to 48 hours after the initiation of thrombolytic therapy. These results indicate that routine immediate angiography and PTCA are not required after administration of rt-PA to patients with acute myocardial infarction.

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